FREEDOM OF INFORMATION SUMMARY

JAN 12 2001

NEW ANIMAL DRUG APPLICATION

NADA 094-170

PHENYLBUTAZONE TABLETS 200 MG

For the relief of inflammatory conditions associated with the musculoskeletal system in dogs.

Sponsored by:

PHOENIX SCIENTIFIC, INC.

NADA 094-170

FOIS-

HFA-305

TABLE OF CONTENTS

FREEDOM OF INFORMATION SUMMARY

Supplement to NADA 094-170 -Phenylbutazone tablets 200mg

1. GENERAL INFORMATION:

NADA Number:	094-170
NADA Sponsor:	Phoenix Scientific, Inc. 3915 South 48th Street Terrace P.O. Box 6457 St. Joseph, MO 64506-0457
Generic Name:	Phenylbutazone Tablets
Trade Name:	Phenylbutazone Tablets USP 200 mg
How Dispensed:	Rx
Effect of Supplement:	To provide for a 200 mg phenylbutazone tablet

2. INDICATIONS FOR USE:

For relief of inflammatory conditions associated with the musculoskeletal system in dogs.

3. DOSAGE:

ORALLY 20 mg/lb. of body weight (200 mg/10 lb.) in three divided doses daily. Maximum dose is 800 mg per day regardless of weight.

Use a relatively high dose for the first 48 hours, then reduce gradually to a maintenance dose.

Maintain lowest dose capable of producing desired clinical response.

4. EFFECTIVENESS:

The 200 mg tablet is identical to the previously approved 100 mg tablet with respect to its excipients and the proportion of active to inactive ingredients. The sole differences between the two formulations are tablet strength and shape.

Since phenylbutazone is a 'Class II' (low solubility, high permeability)

compound [refer to Amidon, GL., Lennernas, H., Shah, VP, and Crison, JR (1995). A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and in vivo bioavailability. *Pharm. Res.*, 12: 413-420], and given the similarity in the approved and proposed tablet formulations, it was determined that comparative *in vitro* dissolution data could provide a surrogate for the demonstration of *in vivo* bioequivalence. Accordingly, in lieu of *in vivo* bioequivalence testing, an *in vitro* comparison was generated for the two tablet sizes (FDA Guidance for Industry – August 1997-Dissolution Testing of Immediate Release Solid Oral Dosage Forms) at Phoenix Scientific, Inc.

Dissolution testing was conducted on 12 units of the 100 mg and 200 mg strength tablets. Samples were collected from each vessel in each dissolution test at 10, 12.5, 15, 17.5, 20, 25, 30 and 45 minutes.

Percent Dissolved:

Strength		**Times (in minutes)**							
		10.0	12.5	15.0	17.5	20.0	25.0	30.0	45.0
100mg									
	Average	55.84	64.09	70.24	75.23	79.20	85.52	90.36	99.62
	%CV	13.6	11.0	7.8	6.6	5.1	4.3	3.6	3.3
200mg									
	Average	64.94	69.80	75.19	80.38	83.58	88.81	92.88	98.90
	%CV	12.0	8.9	8.0	6.8	5.5	4.3	3.7	2.7

As per the FDA/CDER guidance, the assessment of profile comparability was achieved through estimation of the similarity factor (f_2). The f_2 metric is a logarithmic reciprocal square root transformation of the sum of squared error that provides a measure of the similarity in the percent dissolved between two curves and is calculated as follows:

$$f_2 = 50 * \log\{[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)]^{-0.5} * 100\}$$

where n = number of time points
R_t = dissolution value of the reference batch at time t
T_t = the dissolution value of the test batch at time t.

Restrictions associated with the use of the f_2 estimate include:

- The dissolution measurements of the test and reference batches must be

made under exactly the same conditions.

- There should only be one measurement considered after either product has achieved 85% dissolution.
- The percent coefficient of variation at the earliest points (e.g., 15 minutes) should not exceed 20%, and the %CV should not exceed 10% at all other time points.

In keeping with these constraints, the 30 and 45 minute results were not considered in the estimation of the similarity factor. Furthermore, the coefficients of variation associated with the 10 and 12.5 minute samples were less than 20% and the coefficients of variation for the 15 to 25 minute samples were less than 10%. Finally, the test and reference batches were made under exactly the same conditions. Therefore, all restrictions associated with the use of the f_2 criteria for the profile comparison were met.

For this dataset, the Similarity Factor (f_2) = 61.80

For curves to be considered similar, the f_2 value should be greater than or equal to 50. This critical value was achieved, indicating that the change in tablet size from 100 mg to 200 mg did not significantly affect the dissolution of the formula. Accordingly, since phenylbutazone is a Class II compound, these data confirm that the rate and extent of phenylbutazone *in vivo* absorption from the 100 mg and 200 mg strength tablets will be comparable when administered in the same mg/kg b.w. dose.

5. ANIMAL SAFETY:

The 200 mg tablet is the same formula as the previously approved 100 mg tablet but produced as a larger tablet of twice the weight as discussed under **effectiveness.** Refer to NADA 094-170 original Freedom of Information Summary dated January 1, 1974.

6. HUMAN SAFETY:

Human Safety Relative to Food Consumption: Data on human food safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA supplement. This drug is to be labeled for the use in dogs, which are non-food animals.

Human Safety Relative to Possession, Handling and Administration: Labeling contains adequate caution/warning statements.

7. AGENCY CONCLUSIONS:

Data in support of this supplement to NADA 094-170 comply with the requirements of Section 512 of the Act and Section 514 of the implementing regulations. The data demonstrate that 200 mg Phenylbutazone Tablets, when used under labeled conditions are safe and effective for its intended use.

Phenylbutazone Tablets are restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine when a dog has an inflammatory condition associated with the musculoskeletal system warranting the use of such a drug and monitoring its safe use.

Under section 512(c)(2)(F)(iii) of the FFDCA, this approval for non-food producing animals qualifies for three years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies to only the 200 mg tablet, for which the supplemental application was approved.

8. Labeling (Attached)

A.Bottle Label

B.Package Insert

See package insert for dosage and full prescribing information.

INDICATIONS: For relief of inflammatory conditions associated with the musculoskeletal system in dogs.

ADMINISTRATION AND DOSAGE:
ORALLY — 20 mg per lb of body weight (200 mg/10 lb) in three divided doses daily. Maximum dose is 800 mg per day regardless of weight.

Use a relatively high dose for the first 48 hours, then reduce gradually to a maintenance dose.

Maintain lowest dose capable of producing desired clinical response.

801025 Iss. 1-99

Lot No.

Exp. Date

NDC 59130-724-34

PHENYLBUTAZONE TABLETS, USP 200 mg

ANTI-INFLAMMATORY

For Oral Use In Dogs Only

KEEP OUT OF REACH OF CHILDREN

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 94-170, Approved by FDA

NET CONTENTS: 100 TABLETS

AmTech® Group, Inc.

EACH TABLET CONTAINS:
Phenylbutazone, USP . . . . . 200 mg

DISPENSE in a tight container with child resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 20° TO 25°C (68° TO 77°F)

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

TAKE TIME OBSERVE LABEL DIRECTIONS

See package insert for dosage and full prescribing information.

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TAKE TIME OBSERVE LABEL DIRECTIONS

Ok 1/22/99 ok 1/25/99
ok 1/22/99
ok 1-25-99 ok 1-25-99

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: Phoenix Scientific **P.O. #:** Lisa

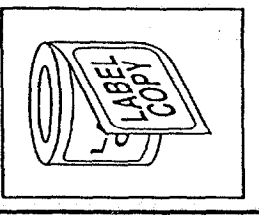
CYREL #: 25917 (sh) **Date Sent:** 1/13/99 1/20/99

LABEL: Phenylbutazone Tablets **UNWIND #:** 4

SIZE: 2" x 6"

PATTERN VARNISH: water

COLORS: 1797 red black



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Approved by: _____ **Date approved:** _____

See package insert for dosage and full prescribing information.

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801025 Iss. 1-99

Lot No.

Exp. Date

NDC 59130-724-21

PHENYLBUTAZONE TABLETS, USP 200 mg

ANTI-INFLAMMATORY

For Oral Use In Dogs Only

KEEP OUT OF REACH OF CHILDREN

CAUTION: Federal law restricts this drug to use by or on the order of a licensed veterinarian.

NADA 94-170, Approved by FDA

NET CONTENTS: 500 TABLETS

AmTech® Group, Inc.

EACH TABLET CONTAINS:
Phenylbutazone, USP . . . . . 200 mg

DISPENSE in a tight container with child resistant closure.

STORE AT CONTROLLED ROOM TEMPERATURE 20° TO 25°C (68° TO 77°F)

Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

TAKE TIME  OBSERVE LABEL DIRECTIONS

See package insert for dosage and full prescribing information.

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801025 Iss. 1-99

Lot No.

Exp. Date

NDC 59130-724-21

PHENYLBUTAZONE TABLETS, USP 200 mg

ANTI-INFLAMMATORY

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NADA 94-170, Approved by FDA

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Manufactured by
Phoenix Scientific, Inc.
St. Joseph, MO 64503

TAKE TIME OBSERVE LABEL DIRECTIONS

1-28-99 c331-29-99
lc 1/27/99 1/28/99
Cf 1/28/99

CUSTOMER PROOF • CHECK CAREFULLY!

Customer: Phoenix Scientific P.O. #: Lisa

CYREL #: 25926 (sh) Date Sent: 1/14/99 1/22/98 _____ _____ _____ _____

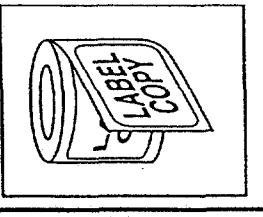
LABEL: Phenylbutazone Tablets0 UNWIND #: 4

SIZE: 2" x 6"

PATTERN VARNISH: water

COLORS: 1797 red black _____ _____

_____ _____ _____ _____



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Approved by: _____ Date approved: _____

NADA 94-170, Approved by FDA

PHENYLBUTAZONE TABLETS, USP

200 mg

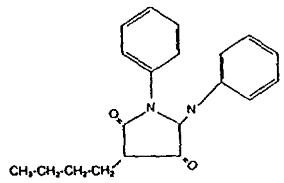
FOR ORAL USE IN DOGS ONLY

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

Phenylbutazone is a synthetic, non-hormonal anti-inflammatory compound useful in the management of inflammatory conditions. The apparent analgesic effect is probably related to the compound's anti-inflammatory properties.

Chemically, Phenylbutazone is 4-butyl-1,2-diphenyl-3,5-pyrazolidinedione. It is a pyrazolon derivative, entirely unrelated to the Steroid hormones, and has the following structural formula:



BACKGROUND PHARMACOLOGY

Kuzell, (1,2,3) Payne, (4) Fleming, (5) and Denko, (6) demonstrated clinical effectiveness of Phenylbutazone in acute rheumatism, gout, gouty, arthritis, and various other rheumatoid disorders in man. Anti-inflammatory activity has been well established by Fabre, (7), Domenjoz, (8) Wilhelmi, (9) and Yourish, (10).

Lieberman (11) reported on the effective use of phenylbutazone in the treatment of painful conditions of the musculoskeletal system in dogs. Joshua (12) observed objective improvement without toxicity following long term therapy of two aged arthritic dogs. Ogilvie and Sutter (13) reported rapid response to phenylbutazone therapy in a review of 19 clinical cases including arthritis, rheumatism, and other conditions associated with lameness and musculoskeletal weakness. Camberos (14) reported favorable results with phenylbutazone following intermittent treatment of Thoroughbred horses for arthritis and chronic arthrosis (e.g., osteoarthritis of medial, and distal bones of the hock, arthritis of stifle and hip, arthrosis of the spine, chronic hip pains, chronic pain in trapezius muscles, and generalized arthritis). Results were less favorable in cases of traumatism, muscle rupture, strains, and inflammations of the third phalanx. Sutter (15) reported favorable response in chronic equine arthritis, fair results in a severely bruised mare, and poor results in two cases where the condition was limited to the third phalanx.

INDICATIONS

For relief of inflammatory conditions associated with the musculoskeletal system in dogs.

CONTRAINDICATIONS

Animals showing evidence of cardiac, hepatic, or renal damage or a history of blood dyscrasia, or those with signs or history of anemia.

PRECAUTIONS

Stop medication at first sign of gastrointestinal upset, jaundice, or blood dyscrasia. Authenticated cases of agranulocytosis associated with the drug have occurred in man; fatal reactions, although rare, have been reported in dogs after long-term therapy. To guard against this possibility, conduct routine blood counts at weekly intervals during the early phase of therapy and at intervals of two weeks thereafter. Any significant fall in the total white count, relative decrease in granulocytes, or black or tarry stools, should be regarded as a signal for immediate cessation of therapy and institution of appropriate counter measures.

In the treatment of inflammatory conditions associated with infections, specific anti-infective therapy is required.

ADMINISTRATION AND DOSAGE

ORALLY—20 mg per lb of body weight (200 mg/10 lb) in three divided doses daily. Maximum dose is 800 mg per day regardless of weight. Use a relatively high dose for the first 48 hours, then reduce gradually to a maintenance dose. Maintain lowest dose capable of producing desired clinical response.

GUIDELINES TO SUCCESSFUL THERAPY

1. Response to Phenylbutazone therapy is prompt, usually occurring within 24 hours. If no significant clinical response is evident after 5 days, re-evalutate diagnosis and therapeutic approach.
2. In animals, Phenylbutazone is largely metabolized in 8 hours. It is recommended that a third of the daily dose be administered at 8 hour intervals. Reduce dosage as symptoms regress. In some cases, treatment may be given only when symptoms appear with no need for continuous medication. If long term therapy is planned, oral administration is suggested.
3. In many cases, tablets may be crushed and given with feed.
4. Many chronic conditions will respond to Phenylbutazone therapy, but discontinuance of treatment may result in recurrence of symptoms.
5. The duration of treatment will depend upon the degree of severity of the condition and generally ranges from 6 to 14 days with retreatment given only to control recurring symptoms. If there is no improvement in 5 days, discontinue treatment.

HOW SUPPLIED

Phenylbutazone Tablets, USP 200 mg are supplied in bottles of 100 and 500 tablets.

Store at controlled room temperature, 20° to 25°C (68° to 77°F).

REFERENCES

1. Kuzell, W.C., Schaffarzick, R.W., Naugler, W.G., and Mankle, E.A.: A.M.A. Arch. Int. Med. 92:646, 1953
2. Kuzell, W.C., Schaffarzick, R.W., Brown, B., and Mankle, E.A.: Jour. Amer. Med. Assoc. 149:729, 1952
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801025 Iss. 1-99

Manufactured By
Phoenix Scientific, Inc.
St. Joseph, MO 64503

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CUSTOMER PROOF • CHECK CAREFULLY!

Customer: Phoenix Scientific

Cyrel#: 25916 (sh) Date Sent: 1/13/99 1/14/99 1/20/99

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